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Clinical features associated with linezolid resistance among multidrug resistant tuberculosis patients at a tertiary care hospital in Mumbai, India

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is an increasing problem worldwide, and 24% occurs in India. Linezolid is associated with improved MDR-TB treatment outcomes but causes significant side-effects and drug susceptibility testing (DST) is rarely available. This study assessed whether clinical factors could predict linezolid resistance.

Methods: An observational cohort of adults and adolescents with MDR-TB at a tertiary care hospital in Mumbai, India was analyzed for clinical, laboratory, and radiographic findings associated with linezolid resistance.

Results: In total, 343 MDR-TB patients had linezolid DST performed, and 23 (6.7%) had linezolid-resistant MDR-TB. Univariable analysis associated linezolid resistance with underweight (odds ratio (OR)–1.07, 95% confidence interval (CI):1.01–1.12); number of previous providers (OR:1.03, 95% CI:1.00–1.05); previous treatment with linezolid (OR:1.12, 95% CI:1.06–1.05), bedaquiline (OR:1.55, 95% CI:1.22–1.98), or clofazimine (OR:1.08 95% CI:1.03–1.16); cavitary disease (OR:1.10, 95% CI:1.04–1.16) and percent lung involvement (OR:1.02, 95% CI:1.01–1.03) on radiograph. DST associated linezolid resistance with resistance to fluoroquinolones (OR:1.08, 95% CI:1.01–1.14), injectables (OR:1.09, 95% CI:1.03–1.15), ethionamide (OR:1.09, 95% CI:1.03–1.15), and PAS (OR:1.13, 95% CI:1.06–1.21). In multivariate analysis, only prior linezolid and percent lung involvement were associated with linezolid resistance.

Conclusion: To maximize treatment benefits while minimizing toxicity, DST remains an important tool to identify linezolid resistance.

1. Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent.[1] Approximately 10 million people contract TB every year, 27% of which occur in India. Reported rates of multidrug resistant (resistance to isoniazid and rifampin, "MDR") and extensively drug resistant (MDR resistant to fluoroquinolones and second-line injectable drugs, "XDR") are rising, affecting 558,000 people worldwide in 2017. Nearly half were in 3 countries, with 24% of reported drug-resistant TB found in India.[1] People can develop MDR/XDR-TB through either inadequate treatment or primary infection with drug-resistant strains of *Mycobacterium tuberculosis* ("*Mtb,*" the bacterium that causes TB), as occurs for most resistant TB in South Africa.[2] While many countries have developed guidelines for treatment of MDR/XDR-TB, additional resistance such as that found in Mumbai often requires an individualized approach to find drugs to which a particular isolate is
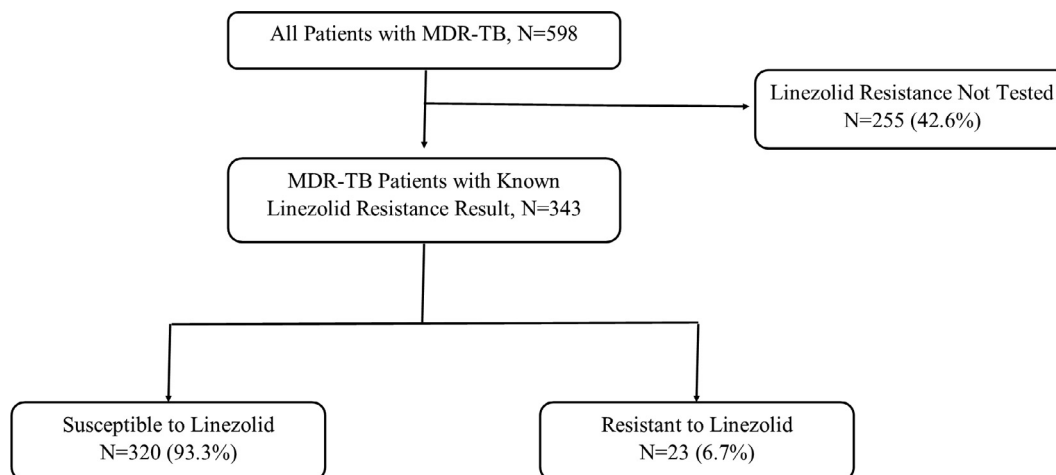
susceptible.[3,4] Constructing treatment regimens for resistant TB is difficult, requiring a balance of efficacy, toxicity, and expense with limited trial evidence available to support specific regimens for complex resistance. In this context, significant attention has been paid to new and repurposed drugs such as linezolid.[5]

Linezolid is an oxazolidinone antibiotic with potent bacteriostatic activity, good penetration into lungs, infected tissue, and CSF,[6,7] and is associated with improved TB treatment outcomes.[8] Following early clinical successes, WHO guidelines have prioritized linezolid, and linezolid is a component of several ongoing clinical trials of TB treatment.[5,9–11] Unfortunately, linezolid therapy is also complicated by serious side effects including painful peripheral neuropathy, vision-threatening optic neuritis, myelosuppression, and drug interactions.[12] In addition, linezolid resistance–while rare–has been reported in multiple countries.[13–15] Few mycobacterial laboratories can perform drug susceptibility testing ("DST") for linezolid, so most TB patients

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Fig. 1. Observational Cohort Study Schema. Participants were recruited from a tertiary care chest clinic in Mumbai. Adults and adolescents with multidrug resistant tuberculosis ("MDR-TB," resistant to rifampin and isoniazid) were recruited to an observational cohort. All participants with linezolid resistance test results available were included for analysis in this manuscript.

receive linezolid without confirmed susceptibility. In this context, it would be helpful to know which clinical factors should lead clinicians to suspect linezolid resistance and prioritize DST. To maximize the benefit to patients of linezolid treatment and minimize unnecessary toxicity, we performed a cross-sectional analysis of MDR-TB patients in Mumbai, India to determine if clinical factors present at the start of treatment were associated with linezolid resistance.

2. Methods

2.1. Study setting

The study was carried out at the P.D. Hinduja National Hospital and Medical Research Centre ("Hinduja Hospital"), a private, tertiary care hospital in Mumbai, India with an outpatient chest clinic and a myco-bacteriology laboratory that performs extensive DST. The outpatient clinic sees ~ 3,000 adults annually, and the lab processes > 32,000 samples for *Mtb* each year. In addition to smear, Xpert MTB/RIF, line probe assays, and pyrosequencing, phenotypic testing at Hinduja Hospital includes mycobacteria growth indicator tube (MGIT) DST for isoniazid, rifampin, pyrazinamide, ethambutol, ofloxacin, moxi-floxacin, amikacin, kanamycin, capreomycin, ethionamide, *para*-ami-nosalicylic acid ("PAS"), clofazimine, and linezolid (1 μg/mL).[16]

2.2. Study design

From October 20, 2015 to July 20, 2019, adults and adoles-cents ≥ 15 years old seeking care for MDR-TB at the Hinduja Hospital chest clinic were enrolled in an observational clinical cohort approved by the Institutional Review Boards of Hinduja Hospital and Johns Hopkins University. After providing written informed consent or (for participants 15–18 years old) written guardian consent and participant assent, each participant's medical records were reviewed. Variables collected included participant demographics (age, sex, self-reported tobacco use, height, weight, and known TB contacts), site of TB (de-fined as pulmonary or extrapulmonary, not mutually exclusive), diag-nosis history (public or private sector, number of prior providers, and months between symptom onset and TB diagnosis), self-reported his-tory of prior TB (defined as completion of treatment followed by ≥ 6 symptom-free months), treatment prescribed prior to enrolment, la-boratory and imaging studies (glycosylated hemoglobin, HIV test re-sults, percentage of lung affected and presence of a cavity on chest radiograph using a standardized scoring system[17]) and DST results (resistant or susceptible to each drug tested). Diabetes status was

defined as either self-reported diagnosis at the time of enrolment or documented glycosylated hemoglobin > 6.5% during study partici-pation. DST results were considered equivalent if they were performed at Hinduja Hospital or if formal reports including drug concentrations were available from another lab.

2.3. Statistical analysis

Data were collected on paper forms, entered in a Microsoft Access database (Office Professional 365, Microsoft Corporation, Redmond, Washington), and analyzed in R (version 3.5.3, R Core Team, Vienna, Austria). Participants were analyzed if linezolid resistance testing was performed (Fig. 1). Frequency tables were constructed for stratified analysis of each characteristic by linezolid resistance status. Due to the observational nature of this study, not every participant had complete laboratory or radiographic records available for review. In such cases, the denominator is defined as the number with available data for each variable. Differences in proportions of categorical variables were compared by Fisher exact tests and differences in continuous variables were compared by student t-tests with p-values < 0.05 considered statistically significant.

Univariable and multivariable logistic regression models were constructed to measure associations between each characteristic and linezolid resistance. Independent variables were modelled continuously (age, body mass index (height in meters / weight in kg^2, "BMI"), months from symptom to diagnosis, medical providers before enrol-ment, percent lung involvement on initial chest radiograph) and cate-gorically (all others). TB requires treatment with multiple drugs si-multaneously and treatments are provided based on pre-specified regimens.[18] For model simplification, BMI was dichotomized as un-derweight (< 18.5 kg/m^2) or not, and treatment prior to enrolment and resistance profiles were categorized according to WHO drug categories from 2018.[5] Classes assessed included "first line drugs" (isoniazid, rifampin, pyrazinamide, and ethambutol), fluoroquinolones (ofloxacin, levofloxacin, or moxifloxacin at this site) other group A drugs (linezolid and bedaquiline); "second-line injectable drugs" (amikacin, kanamycin, or capreomycin, whose priority status was reduced after many parti-cipants were treated), "group B drugs" (cycloserine and clofazimine); "additional group C drugs" (only ethionamide and PAS, as injectables, pyrazinamide, and ethambutol are presented separately, while dela-manid and carbapenem susceptibility was not tested), and "salvage drugs" (amoxicillin/clavulanate and clarithromycin), which are no longer recommended for TB. Multivariable models were constructed based on literature review and exploratory data analysis and included

Table 1

Clinical characteristics of 343 patients with multidrug-resistant tuberculosis (MDR-TB) and linezolid drug susceptibility test results.

	Participants with Linezolid Resistance (N = 23)	Participants with Linezolid Susceptibility (N = 320)	p-value[1]
Clinical Features			
Age in Years, Median (IQR)[2]	26.0 (21.5–38.0)	27.0 (21.0–35.0)	0.708
Female Sex, N (%)	13 (56.5)	202 (63.1)	0.514
Pulmonary TB,[3] N (%)	21 (91.3)	237 (74.1)	0.079**
Extrapulmonary TB,[3] N (%)	2 (8.7)	71 (22.2)	0.186
Body Mass Index (kg/m^2), Median (IQR)[2]	17.4 (15.8–20.3)	19.8 (16.4–23.4)	0.003*
Underweight (< 18.5 kg/m^2)	13 (65.0)	118 (38.3)	0.031
Months from Symptom to Diagnosis, Median (IQR)[2]	1.0 (1.0–1.8)	1.0 (1.0–2.0)	0.234
Number of Medical Providers Before Susceptibility, Median (IQR)[2]	3.0 (1.5–4.5)	2.0 (1.0–3.0)	0.129
Previous Episode of Tuberculosis, N (%)[4]	4 (17.4)	95 (29.7)	0.243
Known Contact with TB, N (%)[4]	7 (30.4)	96 (30.0)	1.000
Self-Reported Tobacco Use (Current or Former), N (%)[4]	1 (4.3)	30 (9.4)	0.708
Diabetes, N (%)[4]	2 (25.0)	30 (21.0)	0.677
HIV Positive, N (%)[4]	0 (0.0)	2 (0.8)	1.000
Works in Health Care Sector, N (%)[4]	0 (0.0)	18 (5.6)	0.621
Prior Treatments			
Previous Treatment with First-Line Drugs (Isoniazid, Rifampin, Pyrazinamide, and Ethambutol), N (%)	14 (60.9)	243 (75.9)	0.133
Previous Treatment with a Fluoroquinolone, N (%)	15 (65.2)	149 (46.6)	0.089**
Previous Treatment with Linezolid, N (%)	14 (60.9)	79 (24.7)	< 0.001*
Previous Treatment with Bedaquiline, N (%)	2 (8.7)	2 (0.6)	0.024*
Previous Treatment with a Group B Drug (Clofazimine or Cycloserine), N (%)	15 (65.2)	134 (41.9)	0.048*
Previous Treatment with a Second-line Injectable Drug (Amikacin, Kanamycin, or Capreomycin), N (%)	12 (52.2)	127 (39.7)	0.275
Previous Treatment with Another Group C Drug (Ethionamide, Prothionamide, or PAS), N (%)	13 (56.5)	136 (42.5)	0.199
Previous Treatment with a Salvage Drug (Clarithromycin, Amoxicillin/Clavulanate), N (%)	11 (47.8)	58 (18.1)	0.002*
Drug Resistance			
Resistant to First-Line Drugs (Isoniazid, Rifampin, Pyrazinamide, or Ethambutol), N (%)[4]	23 (100.0)	302 (94.4)	0.621
Resistant to Fluoroquinolones (Ofloxacin or Moxifloxacin), N (%)[4]	22 (95.7)	234 (73.1)	0.013*
Resistant to Clofazimine, N (%)[4]	1 (4.3)	4 (1.3)	0.300
Resistant to a Second-line Injectable Drug (Amikacin, Kanamycin, or Capreomycin), N (%)	12 (52.2)	81 (25.3)	0.013*
Resistant to Another Group C Drug (Ethionamide or PAS), N (%)[4]	21 (91.3)	202 (63.1)	0.006*
Radiographic Findings			
% Lung Involvement on Initial Chest Radiograph, Median (IQR)[2]	25.0 (10.0–35.0)	10.0 (0.0–30.0)	0.044*
Bilateral Disease on Chest Radiograph, N (%)	2 (10.0)[4]	21 (7.2)[4]	0.651
Cavitary Disease on Chest Radiograph, N (%)	18 (90.0)[4]	147 (50.7)[4]	< 0.001*

[5]This row presents only resistance to ethionamide and PAS, as the other group C drugs are either represented in other rows (ethambutol and pyrazinamide are first-line drugs, and amikacin is a second-line injectable drug) or are not tested at the study site.

[1] p-value indicates *t*-test for continuous variables and Fisher's exact test for categorical variables

[2] IQR – interquartile range

[3] Pulmonary and extrapulmonary TB not mutually exclusive categories

[4] Due to the observational nature of this cohort, not all participants answered all questions, completed susceptibility testing, radiography, or the entire treatment course. Percentage reflects number of participants with data available, rather than denominator of the entire study group.

* p-value < 0.05

** p-value 0.05–0.10

factors known to be associated with treatment outcomes (site of disease, underweight, extent of pulmonary disease, additional drug resistance), potential confounders (age, sex, number of prior providers, prior treatment). Multivariable models were tested for collinearity by variance inflation factor (VIF), with variables reassessed for inclusion in the final model if VIF was ≥ 2.

3. Results

During the study period, a total of 598 participants with MDR-TB were enrolled. Of these, 343 completed DST for linezolid and 23 were resistant (6.7% of those with DST results, 3.8% of total, Fig. 1). Participants tested for linezolid resistance were young with a median age of 27 (interquartile range, "IQR:" 21–35) and were predominantly female (215 participants, 62.7%). Most had pulmonary TB (258 participants, 75.2%), were diagnosed in the public sector (282, 86.5%) and saw a median of 2 other providers before study enrolment (IQR: 1–3). HIV was uncommon (2 participants, 0.6%), while 31 participants (9.0%) reported tobacco use and 32 had diabetes (21.2% of 151 participants

tested, 9.3% of total). Prior TB was reported by 99 (28.9%) participants and 103 (30.0%) reported a household contact with TB. Underweight was common (39.9% of 328 participants with data), as was cavitary lung disease on chest radiograph (53.2% of 310 participants with radiographs). Of the clinical features assessed, lower BMI, prior treatment with linezolid, bedaquiline, clofazimine, amoxicillin/clavulanate, and clarithromycin were more frequent among participants with linezolid resistance than with linezolid susceptible TB. Similarly, resistance to fluoroquinolones, injectable drugs, and group C drugs, and more extensive lung involvement on chest radiograph (percent of lung involved and presence of cavity) were more frequent among those with linezolid resistance (Table 1, Fig. 2). While not statistically significant, pulmonary disease and prior fluoroquinolone treatment were also more common among participants with linezolid resistance.

Regression analysis found higher odds of linezolid resistance among participants who were underweight (odds ratio ("OR"):1.07, 95% confidence interval ("CI"):1.01–1.12), were seen by a greater number of medical providers before diagnosis (OR:1.03, 95% CI:1.00–1.05), were previously treated with group A (OR:1.12, 95% CI:1.06–1.19 for
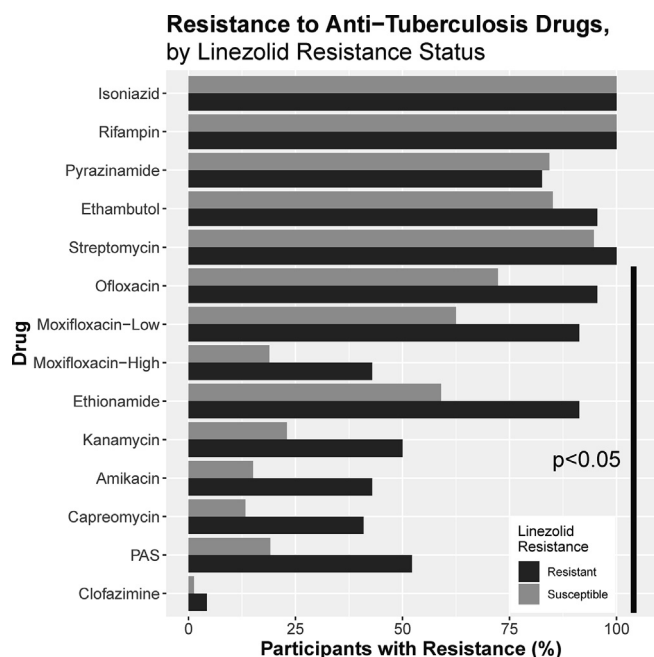
Fig. 2. Resistance to Anti-Tuberculosis Drugs by Linezolid Resistance Status. Rates of resistance to additional drugs on drug susceptibility testing by mycobacterial growth indicator tube identified frequent resistance to other drugs. Rates of resistance to amikacin, kanamycin, capreomycin, ofloxacin, moxifloxacin, ethionamide, and PAS were all statistically significantly different according to linezolid resistance status (p < 0.05).

linezolid, OR:1.55, 95% CI:1.22–1.98 for bedaquiline), group B (OR:1.06, 95% CI:1.01–1.12), or salvage drugs (OR:1.12, 95% CI:1.05–1.20, Table 2). Linezolid resistance was also associated with resistance to fluoroquinolones (OR: 1.08, 95% CI:1.01–1.14), injectable drugs (OR:1.09, 95% CI:1.03–1.15), ethionamide (OR:1.09, 95% CI:1.03–1.15), and PAS (OR:1.13, 95% CI:1.06–1.21). In addition, extent of pulmonary disease was associated with odds of linezolid resistance, either measured by percent lung involvement (OR:1.02, 95% CI:1.01–1.03) or cavitary lung disease (OR:1.10, 95% CI:1.04–1.16). While not statistically significant, increased odds of linezolid resistance were also associated with pulmonary TB (OR 1.06, 95% CI 1.00–1.13) and prior fluoroquinolone treatment (OR 1.05, 95% CI 0.99–1.10). Importantly, a history of prior TB, duration of symptoms before starting treatment, known TB contact, tobacco use, comorbid diabetes, and employment in the health sector were not associated with linezolid resistance. Adjusted multivariable regression analysis found that only prior linezolid treatment (OR:1.10, 95% CI:1.02–1.20) and percent lung involvement on chest radiograph (OR:1.02, 95% CI:1.00–1.04) were significantly associated with linezolid resistance.

4. Discussion

This large, single-site study of 343 participants with MDR-TB and linezolid resistance testing had several important findings. Among this young, female-predominant MDR-TB cohort with high rates of prior treatment and known TB contacts, 6.7% of *Mtb* isolates that completed DST were resistant to linezolid. We found increased odds of linezolid resistance among participants with more severe disease indicated by underweight, extent of lung disease on chest radiograph, and cavitary lung disease. Increased odds of linezolid resistance were also associated with extent of prior treatment indicated by number of previous medical providers and prior treatments received. Similarly, odds of resistance were increased in association with resistance to other drugs, particularly among pre-XDR and XDR *Mtb* isolates, as well as those that were resistant to either ethionamide or PAS. Importantly, a history of prior

TB, duration of illness prior to treatment, known TB contact, tobacco use, and comorbid diabetes were not associated with odds of linezolid resistance. In multivariable analysis, only percent of lung involvement on chest radiograph and prior linezolid treatment remained significant predictors of linezolid resistance.

As rates of MDR- and XDR-TB rise, clinicians in high-burden areas will need improved tools to determine which patients are most likely to benefit from new and repurposed drugs like linezolid. Between excellent distribution throughout the body,[6,7] its in-vitro synergy with bedaquiline, fluoroquinolones, amikacin, and clofazimine,[19–21] and its association with improved treatment outcomes,[22] there are many reasons to include linezolid in treatment regimens for drug-resistant TB. At the same time linezolid is often prescribed for several months outside of clinical trials (median 300 days in *meta*-analysis), and neurologic and hematologic toxicities impacting nearly 60% of treated patients.[23,24] A recent study of 26 weeks of bedaquiline, pretomanid, and linezolid (1200 mg total daily) demonstrated favorable outcomes among 90% of participants, though 81% developed peripheral neuropathy and only 15% completed treatment without linezolid interruption or dose reduction.[25] In the absence of clinical means to predict horrible side effects like optic neuropathy,[26] it is important to identify resistance promptly and appropriately adjustment treatment strategy to prevent unnecessary harm.

Unfortunately, increased use has not been associated with increased global DST capacity for linezolid, so many new prescriptions will occur without confirmation of linezolid susceptibility. This is important, considering increasing recognition of circulating linezolid resistance. The rate of linezolid resistance identified among *Mtb* isolates in this study (6.7% of tested isolates) is similar to rates reported in other areas with high prevalence of drug resistance such as Beijing (5.6%) and Karachi (5.9%), though other studies have reported linezolid resistance rates as high as 10.8% among MDR-TB isolates.[14,15,27] While the number of participants that developed linezolid resistance during treatment is too low in this study for extensive analysis, the importance of testing is further underscored by the published association between linezolid resistance and treatment failure.[28]

Few data on clinical predictors of linezolid resistance are available. In our study, while the minority of participants who received linezolid treatment prior to enrolment were found to have linezolid-resistant isolates (14 out of 93, 15.1%), prior treatment with linezolid was associated with increased odds of linezolid resistance in both univariable and multivariable regression models. This is consistent with previous reports of linezolid resistance among patients previously treated with linezolid.[29] Similarly, in univariable analysis (but not multivariable analysis), we saw increased odds of linezolid resistance associated with resistance to fluoroquinolones, second-line injectable drugs, ethionamide, and PAS. While these results were not significant in multivariable analysis, an association between resistance to linezolid and resistance to fluoroquinolones and injectables has been reported before, though not in association with ethionamide, and PAS resistance.[30] In sensitivity analysis, we did not find significant correlation between resistance to various TB drugs (Pearson correlation coefficient 0.16–0.34 between each drug assessed), however it is reasonable to expect linezolid resistance to follow resistance to first-line drugs, fluoroquinolones, and injectable drugs.[31,32] This is also consistent with the tendency of clinicians to add more drugs to a treatment regimen as resistance is identified,[28] which may explain our findings associating linezolid resistance with a greater number of providers and treatments prior to study enrolment – particularly salvage therapies like amoxicillin/clavulanate and clarithromycin. Finally, cavitary lung disease was more common among participants with linezolid resistance in this study. Linezolid treatment of MDR-TB has been associated specifically with cavity closure,[33] so it is possible that the increased rates of cavitary disease among those with linezolid-resistant isolates reflects failure of response to prior treatment.

Our study has several limitations. This single-site study occurred in

Table 2
Unadjusted and Adjusted Odds of Linezolid Resistance.

Variable	Unadjusted Odds Ratio (95% CI[1])	p-value	Adjusted Odds Ratio (95% CI[1])	p-value
Clinical Features				
Age in Years (10-Year Increments)	1.00 (0.98–1.03)	0.655	1.00 (0.97–1.03)	0.979
Female Sex	0.98 (0.93–1.04)	0.528	0.98 (0.91–1.04)	0.467
Pulmonary TB	1.06 (1.00–1.13)	0.065**	0.96 (0.88–1.05)	0.404
Underweight (< 18.5 kg/m^2)	1.07 (1.01–1.12)	0.018*	1.01 (0.94–1.09)	0.727
Months from Symptom to Diagnosis	1.00 (0.99–1.01)	0.441		
Number of Medical Providers Before Enrolment	1.03 (1.00–1.05)	0.024*	1.00 (0.97–1.03)	0.888
Previous Episode of Tuberculosis	0.96 (0.91–1.02)	0.210		
Known Contact with TB	1.00 (0.94–1.06)	0.965		
Self-Reported Tobacco Use (Current or Former)	0.96 (0.88–1.06)	0.418		
Diabetes	1.01 (0.93–1.11)	0.788		
HIV Positive	0.93 (0.66–1.33)	0.703		
Works in Health Care Sector	0.93 (0.83–1.05)	0.244		
Prior Treatments				
Previous Treatment with First-Line Drugs (Isoniazid, Rifampin, Pyrazinamide, and Ethambutol)	0.95 (0.89–1.01)	0.108	0.95 (0.87–1.02)	0.168
Previous Treatment with a Fluoroquinolone	1.05 (0.99–1.10)	0.084**		
Previous Treatment with Linezolid	1.12 (1.06–1.19)	< 0.001*	1.10 (1.02–1.20)	0.020*
Previous Treatment with Bedaquiline	1.55 (1.22–1.98)	< 0.001*		
Previous Treatment with a Group B Drug (Clofazimine or Cycloserine)	1.06 (1.01–1.12)	0.029*		
Previous Treatment with a Second-line Injectable Drug (Amikacin, Kanamycin, or Capreomycin)	1.03 (0.98–1.09)	0.240		
Previous Treatment with Another Group C Drug (Ethionamide, Prothionamide, or PAS)	1.04 (0.98–1.09)	0.191		
Previous Treatment with a Salvage Drug (Clarithromycin, Amoxicillin/Clavulanate)	1.12 (1.05–1.20)	0.001*		
Drug Resistance				
Resistant to First-Line Drugs (Isoniazid, Rifampin, Pyrazinamide, or Ethambutol)	1.07 (0.95–1.21)	0.244		
Resistant to Fluoroquinolones (Ofloxacin or Moxifloxacin)	1.08 (1.01–1.14)	0.016*	1.01 (0.94–1.09)	0.803
Resistant to Clofazimine[2]	1.14 (0.91–1.43)	0.242		
Resistant to a Second-line Injectable Drug (Amikacin, Kanamycin, or Capreomycin)	1.09 (1.03–1.15)	0.005*	1.01 (0.93–1.10)	0.793
Resistant to Another Group C Drug (Ethionamide or PAS)[3]	1.08 (1.02–1.14)	0.006*	1.07 (1.00–1.15)	0.060**
Radiographic Findings				
Lung Involvement on Chest Radiograph (10% Increments)	1.02 (1.01–1.03)	0.008*	1.02 (1.00–1.04)	0.034*
Cavitary Disease on Chest Radiograph	1.10 (1.04–1.16)	0.001*	1.06 (0.98–1.15)	0.120
Bilateral Disease on Chest Radiograph	1.02 (0.92–1.14)	0.650		

[1] CI: confidence interval

[2] Susceptibility testing for cycloserine is not routinely performed. This represents all susceptibility testing for group B drugs.

[3] This row presents only resistance to ethionamide and PAS, as the other group C drugs are either represented in other rows (ethambutol and pyrazinamide are first-line drugs, and amikacin is a second-line injectable drug) or are not tested at the study site.

* p-value $<$ 0.05

** p-value 0.05–0.10

Mumbai, where circulating drug resistance is common. We have previously reported high rates of resistance to these drugs even among untreated study participants.[4] In this setting, it is possible that the rates of drug resistance identified, the frequency with which DST is performed, and the resulting prescription of other drugs prior to enrollment are higher than among populations with lower rates of drug resistance. Additionally, this cross-sectional dataset did not have sufficient power to report on factors impacting final treatment outcomes, as only 3 participants (0.9%) developed linezolid resistance and most participants have not been followed long-enough to determine final outcome. Our longitudinal clinical experience with linezolid including side effect profiles has been previously published.[34] As more data are available from this and other studies,[9–11] a deeper analysis of the findings of this study with final treatment outcomes will be helpful to guide linezolid treatment decisions. Similarly, the lack of association in this study between linezolid resistance and either prior episodes of TB or known contacts with TB may reflect the frequency of circulating drug resistance rather than new drug resistance developing within study participants during prior treatment. These data may not be generalizable to people with HIV, who represented $<$ 1% of this cohort and have been underrepresented in many published studies of linezolid treatment efficacy.[35] Finally, the reported rate of resistance (7%) is alarming, but may not reach the threshold at which all programs would initiate universal DST,[36] particularly in light of variation in choice of companion drugs. Considering heterogeneity of experiences between published studies of linezolid, additional data from multiple clinical

settings is warranted to determine the population threshold at which universal DST would need to be implemented to prevent linezolid resistance-associated treatment failure or mortality.

The results of this study indicate that clinical data alone have limited association with linezolid resistance test results, with relatively small increases in adjusted odds of linezolid resistance (1.02–1.10). In order to provide patients with the benefits of linezolid treatment without exposing them to unnecessary toxicity, DST for linezolid remains and important tool. While 7% of participants were found to have linezolid-resistant TB, no readily measured clinical correlates other than prior linezolid treatment and extent of lung disease were associated with linezolid resistance. DST remains an important tool to identify resistance for patients planning TB treatment with linezolid.

CRediT authorship contribution statement

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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